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Evaluating the accessibility and utility of HIV-related point-of-care diagnostics for maternal health in rural South Africa: a study protocol

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ABSTRACT

Introduction: Poor health care access is a major barrier to receiving antenatal care and a cause of high maternal mortality in South Africa. 'Point-of-care' (POC) diagnostics are a powerful emerging healthcare approach to improve healthcare access. This study focuses on evaluating the accessibility and utility of POC diagnostics for maternal health in rural SA primary healthcare clinics, in order to generate a model framework of implementation of POC diagnostic in rural South African clinics.

Method and analyses: We will utilize several research methods, including a systematic review, quasi-experimental, survey, key informant interviews and audits. We will conduct a systematic review and experimental study to determination the impact of POC diagnostics on maternal health in South Africa. We will perform a cross-sectional case study of 100 randomly selected rural primary healthcare clinics in KwaZulu-Natal to measure the context and patterns of POC diagnostics access and utilization by maternal health providers and patients. We will conduct key stakeholder interviews to determination the reasons for POC deficiencies regarding accessibility and utility of HIV-related POC diagnostics for maternal health. We will also conduct a vertical audit to investigate the quality all aspects of POC diagnostic services including diagnostic accuracy in a select number of clinics. Based on the information gathered above, we will propose a model framework for improved implementation of POC diagnostics in rural South African public healthcare clinics. Statistical (Stata-13) and thematic (NVIVO) data analysis will be employed in this study.

Ethics and dissemination: The study protocol was approved by the Ethics Committee of the University of KwaZulu Natal (BE 484/14) and the KwaZulu Natal Department of Health based on the Helsinki declaration (HRKM 40/15). Findings of this study will be disseminated electronically and in print. They will be presented to conferences related to HIV/AIDS, diagnostics, maternal health and health systems strengthening.

Strengths and limitations of this study:

- Study will include all key stakeholders of POC diagnostics in the study setting
- Evaluation will reveal barriers and challenges that need to be address before adoption of new POC diagnostics or scaling up the current POC diagnostics services in the study setting.
- To ensure reliability of results, the evaluation POC test performance will only include PHC clinics that are within close proximity of to the testing laboratory.

Keywords: Point-of-care diagnostics; maternal health outcomes; Primary Healthcare Clinic

INTRODUCTION

South Africa has approximately 6 million HIV-infected people, most of them women with 27% of pregnant women living with HIV (1). Of this, the highest infection rate at 10% higher than the national average as well as HIV prevalence and maternal death rates is seen in KwaZulu-Natal (KZN) province (1). The South African National Strategic Plan (NSP) for HIV, TB and STIs 2012-16 contains important recommendations linked to maternal health and highlights the importance of innovations such as point-of-care diagnostics for improvement of patient outcomes (2). UNICEF reports the need to prioritise the improvement of quality of SA health services at primary care level, ensuring timely referral of patients to higher levels of the health system when necessary (2). There remains a lack of uniformity in SA primary health service distribution resulting in failure to meet the unmet needs of patients in resource-limited settings (3). Research studies have demonstrated the implications of poor access to healthcare services in SA rural communities (4, 5) and the usefulness of POC diagnostics for improvement of healthcare access in rural and resource-limited communities in the developing world (6, 7).

A major advantage of POC diagnostics over standard laboratory testing is the ability to provide rapid results, permitting timely initiation of suitable therapy as well as facilitating linkages to care and referrals (8). POC diagnostics has the potential to improve healthcare services by enabling delivery of pathology testing in settings which have limited access to laboratory infrastructure (8). For these reasons, these diagnostics have the potential to play a major role in revolutionizing the diagnosis, initiation and monitoring of treatment of major global diseases. The clinical impact of POC diagnostics has been shown in a variety of infectious diseases, including HIV/AIDS (8). Consequently, World Health Organisation (WHO) called for new clinical diagnostics methods that are designed to function in setting with limited access to laboratory services (9) leading to an increase in marketing, manufacturing and development of POC diagnostic instruments and reagents for clinical use (10).

The use of POC diagnostics could prevent more than 1.2 million deaths from HIV/AIDS, its co-infections and malaria (11). However, previous research has demonstrated that the availability of health technologies in these settings does not always guarantee patient-centred outcomes (12). Implementation of diagnostic POC tests should be evaluated within a given

context to ensure the utility of these novel technologies developed in high-income countries for use in low income countries (13). Evaluations are needed in developing, low resource settings where pregnant and postnatal HIV positive mothers have poor access to quality healthcare facilities and clinical laboratories (14).

Gaining insight into these barriers is useful for informing POC diagnostic developers, policy makers, clinicians and users to ensure the usefulness of POC diagnostics on improvement of HIV-related maternal mortality in rural resource-limited settings. The current proposed study is aimed at assessing the accessibility and utility of HIV related POC diagnostics used for maternal healthcare in rural KZN PHC clinics.

METHODS

A summary of the methodology employed by this multiphase/component study can be found in Table 1. In this study, we will utilize several research methods to determination the impact of POC diagnostics on maternal health in rural KZN. We define rural as sparsely populated areas in which people farm or depend on natural resources, including the villages and small towns that are dispersed through these areas. In addition, they include the large settlements in the former homelands, created by the apartheid removals, which depend for their survival on migratory labour and remittances.

Overall design

The program evaluation theory is a promising approach to explain how a program produces the desired effects (15-17). This theory argues that effective implementation of a program require gathering of evidence from relevant stakeholder (15, 18). The program evaluation theory involves three distinctive approaches: postpositivism; interpretivism and critical normative science paradigm (19). Adopting the postpostivism paradigm will enable us to rationally deduce research experience and interpreted in to concepts and knowledge (20). The interpretivism paradigm will enable us to contextualise of subjective realities of study participants in terms their experiences of POC diagnostics' challenges and barriers and enable us to attach this to meaning and qualitative evidence (21). The critical normative science paradigm will enable critical analysis of POC diagnostic services in order to determine its merit. Combining the program evaluation theory paradigms, we develop a theoretical framework to guide this study (Figure 1). We will employ data triangulation to increase

confidence and diversity regarding the research data (22, 23). Data for this study will be collected from seven sources: surveys, interviews, record review, DHIS routine data, peer reviewed literature and audits.

Research team and study settings

The evaluation study will be carried out in KZN province, South Africa. KZN is located in the southeast of the country on the coast of the Indian Ocean, shares borders with three other provinces and the countries of Mozambique, Swaziland and Lesotho. KZN is the largest province in SA consisting of 11 districts and 52 municipalities and consists of mix of urban, semi-urban and rural areas. The province has a total population of ~10,694,400 population, of which 86.8% are Black Africans and Zulu speakers (24). A representative subset of maternal health primary healthcare clinics in rural KZN will be sampled for this study.

Data sources, sampling variables and analyses

The full data analysis plan for each objective/component can also be found in Table 1. In this study, various methods of data collection and interpretation will be employed as an integrated form of carrying out the methodological triangulation of sources for collecting the quantitative and qualitative samples (22, 23).

Objective 1: To investigate the typology, supply chain of HIV and MH-related POC diagnostics

Data sources: Survey (Table 2)

Sampling: We will conduct a stratified random sampling of PHCs to ensure generalizability (external validity). A sample size of 100 primary units (PU') has been demonstrated to be an appropriate sample size for this type of facility based survey (25). The most recent (2014) data on PHC head count PHC, professional nurse clinic work days, annual nurse's estimate and average headcount per week was requested from the South African District Health Information Software (DHIS) in order to assign sample strata. Four strata were created based on the above sets. A total of 25 facilities were sampled within each of these strata using probability proportional to size (PPS). Proportionate stratification was implemented to insure that sample size of each stratum is proportionate to the population size of the stratum amongst all 11 KZN districts. The sample size of each stratum is proportionate to the population size of the stratum. Strata sample sizes were determined by the following equation:

$$n_h = (N_h / N) * n$$

where n_h is the sample size for stratum *h*, N_h is the population size for stratum *h*, N is total population size, and n is total sample size. Table 3 shows the sampling frame per district.

Variables and data analysis

Statistical analysis will be employed to determine the variations in the availability of POC diagnostics from the sampled clinics (Table 1). Factors such as distance to the nearest emergency hospital and clinic size in terms of patient volumes and staff numbers will be taken into consideration while analysing results.

Objective 2: To investigate the deficiencies and their causes for HIV-related POC diagnostics for maternal health

Data sources: in-depth interviews

Sampling: clinics with low POC diagnostic availability and usage based on the overall average level of availability and usage of POC diagnostics from the sampled clinics clinic.

Variables: The interviews will be aimed at gaining rich data on patients-centred and staff-centred advantages, barriers, challenges of current HIV-related POC diagnostic services as well as future service needs.

Data analysis: Interviews will be conducted in English. Using a grounded theory approach, key points from each transcript will be marked with a series of codes, which are extracted from the text (26). The codes will be grouped into similar concepts that reflect context about local factors that determine healthcare workers and patients' engagement with POC diagnostics. Field notes from observations will be written about each observation session. The observations will be used to contextualize the interview and focus groups findings and confirm the validity of interpretations. Truthfulness is a critical issue in qualitative research (27). In order to account for this, the researcher will perform a verbatim transcription of all interviews and check transcripts with study participants to seek points of clarification in relation to issues arising from interviews. The researcher will also perform an audit trial for assessing the entire research process. Finally, the identified themes will be validated by the study supervisor.

Objective 3: To investigate the quality management systems emplaced to ensure reliability of the HIV-related POC diagnostics for maternal health in their current setting.

Data sources: Audit and validation test

Sampling: In order to determine reliability of POC diagnostic services in clinics with high availability, accessibility and usability of POC diagnostics, the quality management systems implemented in the clinics to will be assessed against relevant quality indicators as prescribed by the most recent WHO guidelines for POC diagnostics in resource-limited settings, through an audit (28). The audit will include: evaluation of the performance, operational characteristics of the test and linkage to healthcare. To determine reliability of the results produced by PHC clinics WHO standards, a POC diagnostic validation test will be carried out. Full blood samples will be requested from consenting women who will be attending the clinic and receiving a HIV POC diagnostic test for laboratory testing. A validation test will be conducted against the gold standard HIV test, enzyme-linked immunosorbent assay (ELISA) test. The sample size at the required absolute precision level for sensitivity and specificity will be dependent on survey, vertical audit results and clinic size. It will be calculated by Buderer's formula (23) which is demonstrated below:

Sample size (n) based on sensitivity = $\frac{Z^2_{1-\alpha/2} \times S_N \times (1-S_N)}{L^2 \times Prevalence}$ and

Sample size (n) based on the specificity = $\frac{Z^2_{1-\alpha/2} \times S_p \times (1-S_p)}{L^2 \times Prevalence}$

Here, n= required sample size

S_N = anticipated sensitivity

S_p =anticipated specificity

α = size of the critical region (1-α is the confidence level)

$Z_{1-\alpha/2}$ =standard normal deviate corresponding to the specified size of the critical region (α) an

L = absolute precision desired on either side (half-width of the confidence interval) of sensitivity or specificity

Due to lack of laboratory infrastructure in rural and resource-limited KwaZulu Natal and to ensure reliability of the POC performance validation test, only PHC clinics that are within 60km to the testing laboratory will be included in the POC test evaluation. It is anticipated that sensitivity (or specificity) of a given POC test is 80% for detecting a given outcome against the laboratory gold standard, assuming an absolute precision of ±10% and prevalence of outcome in the study population is 27% (29) and based on the average patient headcount per week, then it will be necessary to sample and test 207 study subjects using both the POCT and the laboratory gold standard.

Variables and analysis: Table 1 show variables and analysis for the data obtained from the audit

Objective 4: To determine the impact of HIV-related POC diagnostics on maternal mortality using an interrupted time series study.

Data sources: South African District Health Information Software (DHIS).

Sampling: Retrospective data on rural KZN maternal mortality rate from all KZN districts. The time of POC test implementation in KZN rural clinics will be obtained from the department of health archives.

Variables: The following is an explanation of the method of Wagner et al (30), applied to our practical analysis. Time series of maternal mortality rate will be assessed using segmented negative binomial regression analysis, which is a method of estimating changes in levels and trends in an outcome associated with an intervention (POC diagnostics). The time series regression equation for this model is as follows:

$$\hat{Y}_t = \beta_0 + \beta_1 \text{ x } time + \beta_2 \text{ x intervention} + \beta_3 \text{ x } time\_after\_intervention + e_t$$

- $\hat{Y}_t$ is the outcome (mean number of deaths per quarter)
- *time* indicates the number of quarters)from the start of the series
- *intervention* is the dummy variable taking the values 0 in the pre-intervention segment and 1 in the post intervention segment
- *time_after_intervention* is 0 in the pre-intervention segment and counts the quarters in the post-intervention segment at time t.
- The coefficient β_0 estimates the base level of the outcome (number of deaths) at the beginning of the series
- β_1 estimates the base trend, i.e. the change in outcome per quarter in the pre intervention segment
- β_2 estimates the change in level of deaths on the post intervention segment
- β_3 estimates the change in trend in deaths in the post-intervention segment
- e_t estimates the error

This model will be used to estimate the impact of HIV and MH related POC diagnostics on maternal mortality in rural KZN.

Analysis: Data will be processed and analysed using Stata 13.0 (StataCorp. 2013). Stata Statistical Software: Release 13. College Station, TX: StataCorp L). 95% confidence intervals will be constructed around point estimates.

Objective 5: To evaluate whether introduction POC diagnostics into algorithms for diagnosing maternal patients, reduces the maternal mortality rate in rural sub-Saharan Africa using a systematic review.

The systematic review protocol was developed a priori and was registered in the PROSPERO international prospective register of systematic reviews and accepted for publication by BMJ Open. PROSPERO record: CRD42014015439, available at: (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015439#.VSfoV-_GPug). BMJ Open manuscript ID: bmjopen-2015-008002.R1.

The systematic review will follow recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (31) and the Cochrane Handbook for Intervention Reviews (32). The findings of the systematic review will be disseminated through publication in a peer-reviewed journal and will be formatted according to the specific journal publication guidelines.

Data source: The studies will be selected by evaluation of the inclusion and exclusion criteria. This will be carried out in duplicate and independently by two authors with agreement assessed using kappa statistics.

Variables and analysis: Data obtained from eligible studies will be analysed using Review Manager (*RevMan)* 5.3 software. The generic inverse variance method will be used for meta-analysis of both individually and cluster randomised trials.

Objective 6: To develop a model framework and recommendations for improved implementation of POC diagnostics on SA rural PHCs

Guided by the information gathered from the above objectives, we will propose a model framework for improved implementation of POC diagnostics in rural SA PHCs.

Analyses

Qualitative data analysis

Interviews will be conducted with consenting participants in English. Using a grounded theory approach (26), key points from each transcript will be marked with a series of codes, which are extracted from the text by use of NVIVO software. The codes will be grouped into similar concepts that reflect context about local factors that determine healthcare workers and patients' engagement with POC diagnostics. Field notes from observations will be written about each observation session. The observations will be used to contextualize the interview and focus groups findings and confirm the validity of interpretations.

We will perform a verbatim transcription of all interviews and check transcripts with study participants to seek points of clarification in relation to issues arising from interviews. We will also perform an audit trial for assessing the entire research process. Finally, the identified themes will be validated by the study supervisor. Anticipated themes include: Management; Human resources; Infrastructure; Staff knowledge, skill and attitude; Believes; Stakeholder perception and quantitative data analysis.

Quantitative analysis

Quantitative data will be entered into a project specific Microsoft Access database and extracted manually onto a categorised table. Data will be grouped in two levels, facility level and individual level. Facility level data will include data from clinic audits and PHC clinic nurses. Individual data will include data from patients' test results and POC validation of calibration tests.

All quantitative data will be processed and analysed using Stata 13.0 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp L). Descriptive statistics which include frequency distribution, percentages and percentiles, means and standard deviations and cross-tabulations will be used to describe the characteristics of POC diagnostic service in rural KZN. 95% confidence intervals will be constructed around point estimates given the sampling design.

Inferential statistics will be employed to determine significant differences in the availability of POC diagnostics from the sampled clinics. Standard t-test and ANOVA will be used to compare means across groups while the Pearson chi-.square (χ^2) test will be used for

contingency tables. Factors such as distance to the nearest emergency hospital and clinic size in terms of patient volumes and staff numbers, frequency of use for the diagnostics and level of need for the diagnostics (list of POCT requested by clinic staff during survey) will be taken into account. The reliability and accuracy of the POCT test results versus the laboratory gold standard will be estimated along with 95% confidence intervals. A Kappa statistic of agreement will also be calculated.

Limitations

We will address any missing data using appropriate statistical methods (33). Data can be missed for many reasons, such as on occasions when a participant did not show up to participate in a study; or one group had more participants than another; or a device did not record the data correctly. The nature of missing data will determine the statistical analysis methods to be employed.

We undertook a careful and prolonged planning of the study to reduce or eliminate potential sources of bias including sampling bias, recall bias and reporting bias. Recall bias can be introduced in qualitative the data collection stage of investigation, presenting a major threat to the internal validity and credibility of the study. To overcome this limitation in this study, participants will be provided with enough time before answering the question, to reflect and think through a sequence of events in their professional history. The quality of the evidence reported in the systematic review will be assessed across each outcome measure using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to avoid reporting bias (34).

ETHICS AND DESSEMINATION

Ethical principles and patient informed consent

The study is being conducted in accordance with the Helsinki Declaration. Permission letters were obtained from all study site managers: KZN health district managers and KZN National Health Laboratory manager. Written consent authorization will be obtained from all study participants prior to any study procedures being done. Participants will be given a copy of the consent form for their record. The consent process will be documented. Participation will be voluntary and each subject will be able to drop out at any time for any reason.

Legal principles

All personal data will be eliminated. All electronic data of the complete, coded documents will be saved on a protected server which can only be accessed by the members of the internal study team. The paper for of the document will be stored in archives closed for external persons. Data will be kept anonymised kept strictly confidential in storage for two year post completion of the study. No identifying data will be published.

Dissemination of study findings

With this study, our aim is to influence rural PHC policy by translating research evidence to relevant stakeholders. Knowledge translation would be a key aspect of the study, where we intend to disseminate findings to contribute evidence to inform policy makers regarding guidelines for the adoption of new POC diagnostics devices and possible scaling-up the use of POC diagnostic services, for improvement of HIV and maternal health care in rural resource limited settings.

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Authors' contributions

TPMT, BS and PKD conceptualised, design the study. TPMT produced the first draft of the manuscript. BS and PKD commented on this draft and contributed to the final version. All authors read and approved the final manuscript.

Competing interests

None declared

Ethical approval

The protocol was approved by the University of KwaZulu Natal, Biomedical Research Ethics Committee (Ref: BE484/14) and the KwaZulu Natal Department of Health Ethics Committee (Ref: HRKM 40/15).

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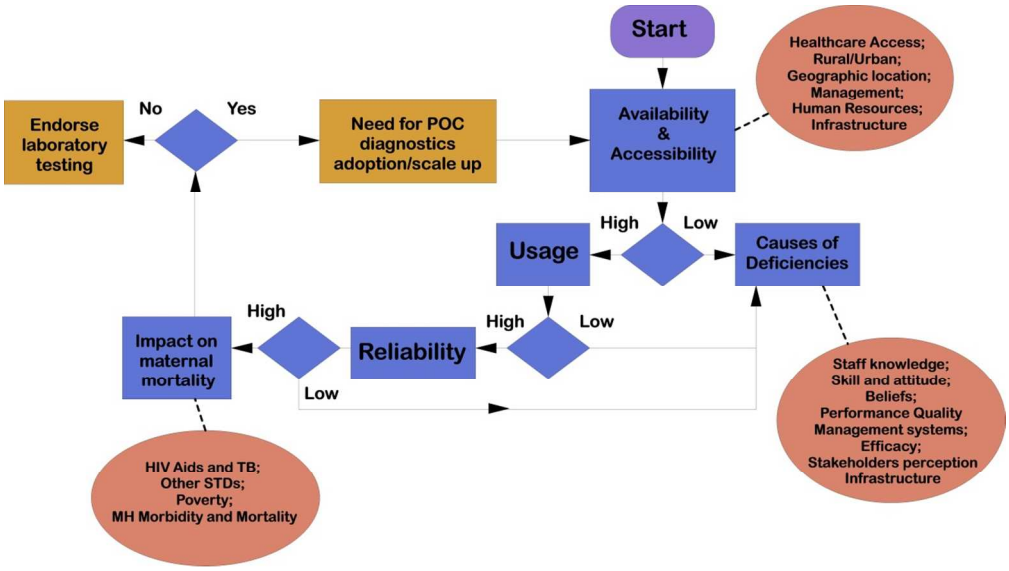

A theoretical framework underpinning this study, program evaluation theory adapted to the local context
152x85mm (220 x 220 DPI)

Objectives	Hypothesis	Study design	Recruitment/ sampling	Independent variable	Dependent variable	Analysis	Outcome measure
To investigate the typology, supply chain of HIV and MH-related POC diagnostics	Improved accessibility of maternal health and HIV-related outcomes can improve effectiveness of maternal health services in rural PHCs	Cross sectional	A total of 100 rural KZN PHCs using probability proportional to size (PPS), stratified into the following: 25 PHCs with high healthcare worker head count; 25 PHCs with low health worker headcount; 25 PHCs with high patient headcount; 25 PHCs with low patient headcount (list of PHCs will be obtained from the SA District Health Information System (DHIS))	Coverage and usage of MH and HIV-related POCT: -Geographic location; District classification (NHI pilot site); Access to tertiary health care	Number and percentage of POC diagnostics	Frequency distribution	Clinics with the highest and lowest POCT availability in each of the 11 districts; Clinic location; Distance between the clinic and nearest town/city; Distance between clinic and nearest referral hospital
				Proportion of facilities that need HIV and MH-related POC diagnostics	Number of diagnostics used		Clinics with the highest and lowest POCT need in each of the 11KZN districts; List of HIV-related POC diagnostics in the clinic; List of HIV-related POC diagnostics needed in the clinic; Laboratory test turn-around-times
				Staff POC diagnostic knowledge and skill assessment	Knowledge of POCT used for diagnosis, monitoring and reduction of referrals		Clinic staff with the highest and lowest POCT knowledge in each of the 11 KZN districts
				Health demand; Availability; Supply chain	Frequency of usage for HIV and MH-related POC diagnostics		List of HIV related POCT available in the clinic; Most and least frequently used POCT in each of the 11 KZN districts; Number of maternal health patients using the clinic; Number of healthcare workers based in the clinics
To investigate deficiencies and their causes in HIV and MH-related POC diagnostics	Demonstrating the causes linked to poor accessibility of maternal health and HIV-related outcomes can help inform and guide implementers during scaling up of current POC services and adoption of new POC services	In-depth interviews	Healthcare workers from PHCs with low availability and usage of POC diagnostics; 11 Public health officials from each (one from each district)	Management; Human resources; Infrastructure; Staff knowledge, skill and attitude; Believes; Stakeholder perception	Improved accessibility, availability and usage and of HIV and MH POCT for maternal health services	Grounded theory	N/A

To investigate the quality management systems (QMS) emplaced to ensure reliability of the HIV and MH-related POC diagnostics in their current setting	Providing evidence on the reliability and sustainability of the QMS for PHC based POCT can provide reassurance to implementers during scaling up of current POC services and adoption of new POC services	Vertical assessment/audit against SANAS ISO 15189:2012 and ISO 22870:2006	Document review from PHCs with high availability and usage of POC diagnostics.	Infrastructure; Quality Management systems; Operational time taken from results reporting to patient treatment for routine cases	Level of quality of service delivery	Correlation coefficient	Overall compliance with relevant ISO standards
			Ease of use	User acceptability		Correlation coefficient	Overall compliance with relevant ISO standards
			Linkage to healthcare	Time from diagnosis to healthcare	Diagnostics turn-around times	Correlation coefficient	Overall compliance with relevant ISO standards
		Efficacy test	Blood samples from maternal health patients who are receiving POC diagnostic services from PHCs with high quality of POC diagnostics service delivery.	Stability of the test under user conditions	Specificity; Sensitivity; Positive and negative likelihood ratios; Positive and negative predictive values	95% coefficient intervals (CI) and paired Z test to compare CI of validation indices (Sensitivity; Specificity; Negative Predictive Value (NPV) and Positive Predictive Value (PPV) Kappa Statistic (k)) between POC diagnostics results and laboratory results	Correlation between the laboratory and POCT results
			The sample size at the required absolute precision level for sensitivity and specificity will be dependent on survey, vertical audit results and clinic size. It will can be calculated by Buderer's formula (23).	Reliability of the POCT results	Accuracy of results in comparison with gold standard (ELISA)	Correlation coefficient	Correlation between the laboratory and POCT results

To determine the impact of HIV and MH-related POC diagnostics on maternal mortality using quasi-experiment	Demonstrating the impact of HIV and MH-related POCT on maternal mortality provides merit/worth for POCT scale up in KZN maternal health clinics	Quasi-experimental , interrupted time series	DHIS data on maternal mortality rate (MMR) data from the PHCs with high quality of POC diagnostics service delivery.	Time aggregation: monthly level, facility level; Facility specific time of implementation of POC diagnostics (syphilis) will be used as a break point of in segmented regression	Change in maternal mortality rate	Segmented regression modelling	Reduction in maternal mortality post POCT implementation.
To evaluate whether introduction POC diagnostics into algorithms for diagnosing maternal patients, reduces the maternal mortality rate in rural sub-Saharan Africa.	Evidence from a systematic review (highest quality of evidence) indicating the impact of HIV-related POCT on maternal outcomes of HIV infected mothers will show significance for POCT scale up in rural and resource limited maternal health clinics	Systematic review and meta-analysis	Peer reviews literature fitting the inclusion and exclusion criteria	HIV-related POCT interventions for maternal health versus other maternal health interventions	Improved maternal outcomes: maternal mortality; prevention of maternal and child transmission and	Meta-analysis	Studies reporting a significant improvement of maternal outcomes
To develop a model framework and recommendations for improved implementation of POC diagnostics on SA rural PHCs	Developing local evidence based frameworks and guidelines can improve the effectiveness of the services	KZN province	N/A	Evidence based guidelines (based on the evidence obtained from the above objectives)	Improved implementation of POC diagnostic services for rural South Africa	N/A	N/A

PHC POC Diagnostics Services Survey tool

District code: District Name:	**Clinic code:**
Clinic contact details:	**Clinic name:**
Assessors name:	**Date:**

A	**Clinic size and staffing**	
A1	Which of the following healthcare professional are in your clinic?	*(Choose from list below)* ○ Drs: number_____ ○ Nurses: Number_____ ○ Specialist Nurse_____ ○ Sisters_____ ○ Other (Specify)_____
A2	Which of the following describe your role?	*(Choose from list below)* ○ Dr ○ Nurse ○ Specialist Nurse ○ Sister ○ Other (Specify)_____
A3	What is an average number of maternal health (antenatal) patients admitted in the clinic per week?	*(Write number)*
A4	How many hours per week do you work (on average)?	*(Write number)*
B	**POC diagnostics service linkage to healthcare**	
B1	How many kilometers to your nearest emergency department that admits patients to hospital?	*(Write number)*
B2	How many kilometers to your nearest town/city?	*(Write number)*
C	**Length of time for blood test**	
C1	How long does it typically take to get results	*(Choose from the following)*

	from a routine blood test, such as full blood count?	○ One day or more: _____days ○ Less than 1 day: _____ hours ○ Already use a POC diagnostics for this test, so it is immediately done
C2	How long does it typically take to get results from a TB sputum test?	*(Choose from the following)* ○ One day or more: _____days ○ Less than 1 day: _____ hours ○ Already use a POC diagnostics for this test, so it is immediately done
D	**Staff POC diagnostics competency**	
D1	What year did you qualify as a Healthcare professional?	*(Write full year)*
D2	Please name up to five conditions which a POC test could help you make a **diagnosis**. Please list the conditions irrespective of whether or not POC test currently exist	○ _____ ○ _____ ○ _____ ○ _____ ○ _____ **I do not think POC tests would help me make a diagnosis (please tick box)** ☐
D3	Please name up to five conditions which a POC test could help you **monitor**. Please list the conditions irrespective of whether or not POC test currently exist	○ _____ ○ _____ ○ _____ ○ _____ ○ _____ **I do not think POC tests would help me monitor a disease (please tick box)** ☐
D4	Please name up to five conditions which a POC	

	test could help you reducing **referrals for specialty care or hospital admission**. Please list the conditions irrespective of whether or not POC test currently exist	○ _____ ○ _____ ○ _____ ○ _____ ○ _____ **I do not think POC tests would help me reduce referrals for specialty care or hospital admission (please box)** ☐

E. POCTs used for HIV and Maternal Health

Please select the answer that best matches your views about current or potential use of point of care tests (POCTs)

	This test **is** currently available as a point of care test (POCT) in my clinic		This test **is not** currently available as a point of care test (POCT) in my clinic	
	(1) I **do** use this test	*(2)* I **do not** use this test	*(3)* I **would** use this test	*(4)* I **would not** use this test
TESTS ON BLOOD				
Cardiovascular				
Creatinine				
Potassium				
Sodium				
Total cholesterol				
HDL/LDL cholesterols				
Triglycerides				
Calcium				
Uric Acid				
BNP (B-natriuretic peptide)				
D-dimer				
Troponin				
Endocrine				
Blood glucose				
HbA1c				
TSH (thyroid stimulating hormone)				
Free T4 or T3				
Haematology				

INR				
Haemoglobin				
White cell count				
Platelet count				
Prothrombin time				
Infection related				
CRP (C-reactive protein)				
Procalcitonin				
HIV blood test				
Syphilis				
Hepatitis B				
Liver				
AST/ALT				
Alkaline phosphatase				
Bilirubin				
Gamma GT (ɣ-glutamyltransferase)				
Albumin				
Other (blood)				
ESR (*Erythrocyte sedimentation rate)*				
CA125				
PSA (Prostate Specific Antigen)				
Vitamin D				
Vitamin B12				
Folate				
Quantitative Beta HCG (Human chorionic gonadotropin)				
Rheumatoid factor				
ANA (anti-nuclear antibodies)				

	This test **is** currently available as a point of care test (POCT) in my clinic		This test **is not** currently available as a point of care test (POCT) in my clinic	
	(1) I **do** use this test	*(2)* I **do not** use this test	*(3)* I **would** use this test	*(4)* I **would not** use this test
RESPIRATORY SAMPLES				
Throat swab for Group A Streptococci				
Nasal swab for MRSA				

Nose/throat swab for influenza				
TESTS ON URINE OR GENITAL FLUIDS				
Urine pregnancy test				
Urine leukocytes or nitrite				
Chlamydia				
Gonorrhoea				
Urine albumin:creatinine ratio				
Urine total protein				
Urine protein:creatinine ratio				
TESTS ON FAECES				
Faecal occult blood				
Faecal calprotectin				
OTHER TESTS WE HAVE NOT LISTED HERE				

F. Frequency of POCT usage for HIV and Maternal Health

Below is a list of point of care tests (POCTS) you indicated that you would use or currently use in your practice. Please tell us how often you would use or do use these

	More than once per day	Daily	Weekly	Monthly	Once per year or less
TESTS ON BLOOD					
Cardiovascular					
Creatinine					
Potassium					
Sodium					
Total cholesterol					
HDL/LDL cholesterols					
Triglycerides					
Calcium					
Uric Acid					
BNP (B-natriuretic					

peptide)					
D-dimer					
Troponin					
Endocrine					
Blood glucose					
HbA1c					
TSH (thyroid stimulating hormone)					
Free T4 or T3					
Haematology					
INR					
Haemoglobin					
White cell count					
Platelet count					
Prothrombin time					
Infection related					
CRP (C-reactive protein)					
Procalcitonin					
HIV blood test					
Syphilis					
Hepatitis B					
Liver					
AST/ALT					
Alkaline phosphatase					
Bilirubin					
Gamma GT (ɣ-glutamyltransferase)					
Albumin					
Other (blood)					
ESR (*Erythrocyte sedimentation rate)*					
CA125					
PSA (Prostate Specific Antigen)					
Vitamin D					
Vitamin B12					
Folate					
Quantitative					

Beta HCG (Human chorionic gonadotropin)					
Rheumatoid factor					
ANA (anti-nuclear antibodies)					

	More than once per day	Daily	Weekly	Monthly	Once per year or less
RESPIRATORY SAMPLES					
Throat swab for Group A Streptococci					
Nasal swab for MRSA					
Nose/throat swab for influenza					
TESTS ON URINE OR GENITAL FLUIDS					
Urine pregnancy test					
Urine leukocytes or nitrite					
Chlamydia					
Gonorrhoea					
Urine albumin:creatinine ratio					
Urine total protein					
Urine protein:creatinine ratio					
TESTS ON FAECES					
Faecal occult blood					
Faecal calprotectin					
OTHER TESTS WE HAVE NOT LISTED HERE					
Do you have suggestions for new POC Tests?					
What POC tests might make your job easier?					

District code	District name	Sample number
B1	Amajuba District Municipality	6
B2	eThekwini Metropolitan Municipality	7
B3	iLembe District Municipality	7
B4	Harry Gwala District Municipality	8
B5	Ugu District Municipality	14
B6	uMgungundlovu District Municipality	4
B7	uMkhanyakude District Municipality	22
B8	uMzinyathi District Municipality	5
B9	uThukela District Municipality	6
B10	uThungulu District Municipality	18
B11	Zululand District Municipality	3

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Evaluating the accessibility and utility of HIV-related point-of-care diagnostics for maternal health in rural South Africa: a study protocol

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Evaluating the accessibility and utility of HIV-related point-of-care diagnostics for maternal health in rural South Africa: a study protocol

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ABSTRACT

Introduction: Poor health care access is a major barrier to receiving antenatal care and a cause of high maternal mortality in South Africa. 'Point-of-care' (POC) diagnostics are a powerful emerging healthcare approach to improve healthcare access. This study focuses on evaluating the accessibility and utility of POC diagnostics for maternal health in rural SA primary healthcare clinics, in order to generate a model framework of implementation of POC diagnostic in rural South African clinics.

Method and analyses: We will utilize several research methods, including a systematic review, quasi-experimental, survey, key informant interviews and audits. We will conduct a systematic review and experimental study to determination the impact of POC diagnostics on maternal health. We will perform a cross-sectional case study of 100 randomly selected rural primary healthcare clinics in KwaZulu-Natal to measure the context and patterns of POC diagnostics access and utilization by maternal health providers and patients. We will conduct interviews with relevant key stakeholders to determination the reasons for POC deficiencies regarding accessibility and utility of HIV-related POC diagnostics for maternal health. We will also conduct a vertical audit to investigate the quality all aspects of POC diagnostic services including diagnostic accuracy in a select number of clinics. Based on the information gathered above, we will propose a model framework for improved implementation of POC diagnostics in rural South African public healthcare clinics. Statistical (Stata-13) and thematic (NVIVO) data analysis will be employed in this study.

Ethics and dissemination: The study protocol was approved by the Ethics Committee of the University of KwaZulu Natal (BE 484/14) and the KwaZulu Natal Department of Health based on the Helsinki declaration (HRKM 40/15). Findings of this study will be disseminated electronically and in print. They will be presented to conferences related to HIV/AIDS, diagnostics, maternal health and health systems strengthening.

Strengths and limitations of this study:

- Study will include relevant key stakeholders of POC diagnostics in the study setting
- Evaluation will reveal barriers and challenges that need to be address before adoption of new POC diagnostics or scaling up the current POC diagnostics services in the study setting.
- To ensure reliability of results, the evaluation POC test performance will only include PHC clinics that are within close proximity of to the testing laboratory.

Keywords: Point-of-care diagnostics; maternal health outcomes; Primary Healthcare Clinic

INTRODUCTION

South Africa has approximately 6 million HIV-infected people, most of them women with 27% of pregnant women living with HIV (1). Of this, the highest infection rate at 10% higher than the national average as well as HIV prevalence and maternal death rates is seen in KwaZulu-Natal (KZN) province (1). The South African National Strategic Plan (NSP) for HIV, TB and STIs 2012-16 contains important recommendations linked to maternal health and highlights the importance of innovations such as point-of-care diagnostics for improvement of patient outcomes (2). UNICEF reports the need to prioritise the improvement of quality of SA health services at primary care level, ensuring timely referral of patients to higher levels of the health system when necessary (2). There remains a lack of uniformity in SA primary health service distribution resulting in failure to meet the unmet needs of patients in resource-limited settings (3). Research studies have demonstrated the implications of poor access to healthcare services in SA rural communities (4, 5) and the usefulness of POC diagnostics for improvement of healthcare access in rural and resource-limited communities in the developing world (6, 7).

A major advantage of POC diagnostics over standard laboratory testing is the ability to provide rapid results, permitting timely initiation of suitable therapy as well as facilitating linkages to care and referrals (8). POC diagnostics has the potential to improve healthcare services by enabling delivery of pathology testing in settings which have limited access to laboratory infrastructure (8). For these reasons, these diagnostics have the potential to play a major role in revolutionizing the diagnosis, initiation and monitoring of treatment of major global diseases. The clinical impact of POC diagnostics has been shown in a variety of infectious diseases, including HIV/AIDS (8). Consequently, World Health Organisation (WHO) called for new clinical diagnostics methods that are designed to function in setting with limited access to laboratory services (9) leading to an increase in marketing, manufacturing and development of POC diagnostic instruments and reagents for clinical use (10).

The use of POC diagnostics could prevent more than 1.2 million deaths from HIV/AIDS, its co-infections and malaria (11). However, previous research has demonstrated that the availability of health technologies in these settings does not always guarantee patient-centred outcomes (12). Implementation of diagnostic POC tests should be evaluated within a given

context to ensure the utility of these novel technologies developed in high-income countries for use in low income countries (13, 14). Evaluations are needed in developing, low resource settings where pregnant and postnatal HIV positive mothers have poor access to quality healthcare facilities and clinical laboratories (15).

Gaining insight into these barriers is useful for informing POC diagnostic developers, policy makers, clinicians and users to ensure the usefulness of POC diagnostics on improvement of HIV-related maternal mortality in rural resource-limited settings. The overarching aim of this study is to evaluate the accessibility, availability and utility of POC diagnostic services for in rural Primary Healthcare clinics in South Africa in order to develop an ideal model framework and recommendations for improved implementation of POC diagnostics in these settings. The following objectives will be outlined in order to address the aim of the study: First, to investigate the typology, supply chain POC diagnostics in rural PHC clinics in South Africa; Second, to investigate the deficiencies and their causes for POC diagnostics in rural PHC clinics in South Africa; Third, to investigate the quality management systems emplaced to ensure reliability of the HIV-related POC diagnostics for maternal health in their current setting; Fourth, to determine the impact of HIV-related POC diagnostics on maternal mortality using an interrupted time series study; Fifth, to evaluate whether introduction POC diagnostics into algorithms for diagnosing maternal patients, improves maternal health for HIV infected women using a systematic review and finally to develop a model framework and recommendations for improved implementation of POC diagnostics on SA rural PHCs

METHODS

A summary of the methodology employed by this multiphase/component study can be found in Table 1. In this study, we will utilize several research methods to determination the impact of POC diagnostics on maternal health in rural KZN. We define rural as sparsely populated areas in which people farm or depend on natural resources, including the villages and small towns that are dispersed through these areas. In addition, they include the large settlements in the former homelands, created by the apartheid removals, which depend for their survival on migratory labour and remittances.

1 **Table 1: Summary of the methodology**

Objectives	Hypothesis	Study design	Recruitment/ sampling	Independent variable	Dependent variable	Analysis	Outcome measure
To investigate the typology, supply chain of HIV and MH-related POC diagnostics	Improved accessibility of maternal health and HIV-related outcomes can improve effectiveness of maternal health services in rural PHCs	Cross sectional	A total of 100 rural KZN PHCs using probability proportional to size (PPS), stratified into the following: 25 PHCs with high healthcare worker head count; 25 PHCs with low health worker headcount; 25 PHCs with high patient headcount; 25 PHCs with low patient headcount (list of PHCs will be obtained from the SA District Health Information System (DHIS))	Coverage and usage of MH and HIV-related POCT: -Geographic location; District classification (NHI pilot site); Access to tertiary health care	Number and percentage of POC diagnostics	Frequency distribution	Clinics with the highest and lowest POCT availability in each of the 11 districts; Clinic location; Distance between the clinic and nearest town/city; Distance between clinic and nearest referral hospital
				Proportion of facilities that need HIV and MH-related POC diagnostics	Number of diagnostics used		Clinics with the highest and lowest POCT need in each of the 11KZN districts; List of HIV-related POC diagnostics in the clinic; List of HIV-related POC diagnostics needed in the clinic; Laboratory test turn-around-times
				Staff POC diagnostic knowledge and skill assessment	Knowledge of POCT used for diagnosis, monitoring and reduction of referrals		Clinic staff with the highest and lowest POCT knowledge in each of the 11 KZN districts
				Health demand; Availability; Supply chain	Frequency of usage for HIV and MH-related POC diagnostics		List of HIV related POCT available in the clinic; Most and least frequently used POCT in each of the 11 KZN districts; Number of maternal health patients using the clinic; Number of healthcare workers based in the clinics
To investigate deficiencies and their causes in HIV and MH-related POC diagnostics	Demonstrating the causes linked to poor accessibility of maternal health and HIV-related outcomes can help inform and guide implementers during scaling up of current POC services and adoption of new POC services	In-depth interviews	Healthcare workers from PHCs with low availability and usage of POC diagnostics; 11 Public health officials from each (one from each district)	Management; Human resources; Infrastructure; Staff knowledge, skill and attitude; Believes; Stakeholder perception	Improved accessibility, availability and usage and of HIV and MH POCT for maternal health services	Thematic analysis	N/A

To investigate the quality management systems (QMS) emplaced to ensure reliability of the HIV and MH-related POC diagnostics in their current setting	Providing evidence on the reliability and sustainability of the QMS for PHC based POCT can provide reassurance to implementers during scaling up of current POC services and adoption of new POC services	Vertical assessment/audit against SANAS ISO 15189:2012 and ISO 22870:2006	Document review from PHCs with high availability and usage of POC diagnostics.	Infrastructure; Quality Management systems; Operational time taken from results reporting to patient treatment for routine cases	Level of quality of service delivery	Correlation coefficient	Overall compliance with relevant ISO standards
			Ease of use	User acceptability		Correlation coefficient	Overall compliance with relevant ISO standards
			Linkage to healthcare	Time from diagnosis to healthcare	Diagnostics turn-around times	Correlation coefficient	Overall compliance with relevant ISO standards
		Efficacy test	Blood samples from maternal health patients who are receiving POC diagnostic services from PHCs with high quality of POC diagnostics service delivery.	Stability of the test under user conditions	Specificity; Sensitivity; Positive and negative likelihood ratios; Positive and negative predictive values	95% coefficient intervals (CI) and paired Z test to compare CI of validation indices (Sensitivity; Specificity; Negative Predictive Value (NPV) and Positive Predictive Value (PPV) Kappa Statistic (k)) between POC diagnostics results and laboratory results	Correlation between the laboratory and POCT results
			The sample size at the required absolute precision level for sensitivity and specificity will be dependent on survey, vertical audit results and clinic size. It will can be calculated by Buderer's formula (16).	Reliability of the POCT results	Accuracy of results in comparison with gold standard (ELISA)	Correlation coefficient	Correlation between the laboratory and POCT results

To determine the impact of HIV and MH-related POC diagnostics on maternal mortality using quasi-experiment	Demonstrating the impact of HIV and MH-related POCT on maternal mortality provides merit/worth for POCT scale up in KZN maternal health clinics	Quasi-experimental , interrupted time series	DHIS data on maternal mortality rate (MMR) data from the PHCs with high quality of POC diagnostics service delivery.	Time aggregation: monthly level, facility level; Facility specific time of implementation of POC diagnostics (syphilis) will be used as a break point of in segmented regression	Change in maternal mortality rate	Segmented regression modelling	Reduction in maternal mortality post POCT implementation.
To evaluate whether introduction POC diagnostics into algorithms for diagnosing maternal patients, reduces the maternal mortality rate in rural sub-Saharan Africa.	Evidence from a systematic review (highest quality of evidence) indicating the impact of HIV-related POCT on maternal outcomes of HIV infected mothers will show significance for POCT scale up in rural and resource limited maternal health clinics	Systematic review and meta-analysis	Peer reviews literature fitting the inclusion and exclusion criteria	HIV-related POCT interventions for maternal health versus other maternal health interventions	Improved maternal outcomes: maternal mortality; prevention of maternal and child transmission and	Meta-analysis	Studies reporting a significant improvement of maternal outcomes
To develop a model framework and recommendations for improved implementation of POC diagnostics on SA rural PHCs	Developing local evidence based frameworks and guidelines can improve the effectiveness of the services	KZN province	N/A	Evidence based guidelines (based on the evidence obtained from the above objectives)	Improved implementation of POC diagnostic services for rural South Africa	N/A	N/A

Overall design

The program evaluation theory is a promising approach to explain how a program produces the desired effects (17-19). This theory argues that effective implementation of a program require gathering of evidence from relevant stakeholder (17, 20). The program evaluation theory involves three distinctive approaches: postpositivism; interpretivism and critical normative science paradigm (21). Adopting the postpostivism paradigm will enable us to rationally deduce research experience and interpreted in to concepts and knowledge (22). The interpretivism paradigm will enable us to contextualise of subjective realities of study participants in terms their experiences of POC diagnostics' challenges and barriers and enable us to attach this to meaning and qualitative evidence (23). The critical normative science paradigm will enable critical analysis of POC diagnostic services in order to determine its merit. Combining the program evaluation theory paradigms, we develop a theoretical framework to guide this study (Figure 1). We will employ data triangulation to increase confidence and diversity regarding the research data (16, 24). Data for this study will be collected from seven sources: surveys, interviews, record review, DHIS routine data, peer reviewed literature and audits.

Research team and study settings

The evaluation study will be carried out in KZN province, South Africa. KZN is located in the southeast of the country on the coast of the Indian Ocean, shares borders with three other provinces and the countries of Mozambique, Swaziland and Lesotho. KZN is the largest province in SA consisting of 11 districts and 52 municipalities and consists of mix of urban, semi-urban and rural areas. The province has a total population of ~10,694,400 population, of which 86.8% are Black Africans and Zulu speakers (25). A representative subset of maternal health primary healthcare clinics in rural KZN will be sampled for this study.

Data sources, sampling variables and analyses

The full data analysis plan for each objective/component can also be found in Table 1. In this study, various methods of data collection and interpretation will be employed as an integrated form of carrying out the methodological triangulation of sources for collecting the quantitative and qualitative samples (22, 23).

Objective 1: To investigate the typology, supply chain POC diagnostics in rural PHC clinics in South Africa.

Data sources: Survey (survey tool has been provided as supplementary file)

Sampling: We will conduct a stratified random sampling of PHC clinics to ensure generalizability (external validity). PHC clinic healthcare professionals responsible for the POC diagnostic services in the clinic will be requested to participate in the survey. A sample size of 100 primary units (PU') has been demonstrated to be an appropriate sample size for this type of facility based survey (26). The most recent (2014) data on PHC head count PHC, professional nurse clinic work days, annual nurse's estimate and average headcount per week was requested from the South African District Health Information Software (DHIS) in order to assign sample strata. Four strata were created based on the above sets. A total of 25 facilities were sampled within each of these strata using probability proportional to size (PPS). Proportionate stratification was implemented to insure that sample size of each stratum is proportionate to the population size of the stratum amongst all 11 KZN districts. The sample size of each stratum is proportionate to the population size of the stratum. Strata sample sizes were determined by the following equation:

$$n_h = (N_h / N) * n$$

where n_h is the sample size for stratum h, N_h is the population size for stratum h, N is total population size, and n is total sample size. Table 2 shows the sampling frame per district.

Table 2: Project sampling frame

District code	District name	Sample number
B1	Amajuba District Municipality	6
B2	eThekwini Metropolitan Municipality	7
B3	iLembe District Municipality	7
B4	Harry Gwala District Municipality	8
B5	Ugu District Municipality	14
B6	uMgungundlovu District Municipality	4
B7	uMkhanyakude District Municipality	22
B8	uMzinyathi District Municipality	5
B9	uThukela District Municipality	6
B10	uThungulu District Municipality	18
B11	Zululand District Municipality	3

Objective 2: To investigate the deficiencies and their causes for POC diagnostics in rural PHC clinics in South Africa

Data sources: in-depth interviews

Sampling: clinics with low POC diagnostic availability and usage based on the overall average level of availability and usage of POC diagnostics from the sampled clinics clinic.

Variables: The interviews will be aimed at gaining rich data on patients-centred and staff-centred advantages, barriers, challenges of current POC diagnostic services as well as future service needs.

Objective 3: To investigate the quality management systems emplaced to ensure reliability of the HIV-related POC diagnostics for maternal health in their current setting.

Data sources: Audit and validation test

Sampling: In order to determine reliability of POC diagnostic services in clinics with high availability, accessibility and usability of POC diagnostics, the quality management systems implemented in the clinics to will be assessed against relevant quality indicators as prescribed by the most recent WHO guidelines for POC diagnostics in resource-limited settings, through an audit (27). The audit will include: evaluation of the performance, operational characteristics of the test and linkage to healthcare. To determine reliability of the results produced by PHC clinics WHO standards, a POC diagnostic validation test will be carried out. Full blood samples will be requested from consenting women who will be attending the clinic and receiving a HIV POC diagnostic test for laboratory testing. A validation test will be conducted against the gold standard HIV test, enzyme-linked immunosorbent assay (ELISA) test. The sample size at the required absolute precision level for sensitivity and specificity will be dependent on survey, vertical audit results and clinic size. It will be calculated by Buderer's formula (16) which is demonstrated below:

Sample size (n) based on sensitivity = $\frac{Z^2_{1-\alpha/2} \times S_N \times (1-S_N)}{L^2 \times Prevalence}$ and

Sample size (n) based on the specificity = $\frac{Z^2_{1-\alpha/2} \times S_p \times (1-S_p)}{L^2 \times Prevalence}$

Here, n= required sample size

S_N = anticipated sensitivity

S_p =anticipated specificity

α = size of the critical region (1-α is the confidence level)

$Z_{1-\alpha/2}$ =standard normal deviate corresponding to the specified size of the critical region (α) an

L = absolute precision desired on either side (half-width of the confidence interval) of sensitivity or specificity

Due to lack of laboratory infrastructure in rural and resource-limited KwaZulu Natal and to ensure reliability of the POC performance validation test, only PHC clinics that are within 60km to the testing laboratory will be included in the POC test evaluation. It is anticipated that sensitivity (or specificity) of a given POC test is 80% for detecting a given outcome against the laboratory gold standard, assuming an absolute precision of ±10% and prevalence of outcome in the study population is 27% (28) and based on the average patient headcount per week, then it will be necessary to sample and test 207 study subjects using both the POCT and the laboratory gold standard.

Objective 4: To determine the impact of HIV-related POC diagnostics on maternal mortality using an interrupted time series study.

Data sources: South African District Health Information Software (DHIS).

Sampling: Retrospective data on rural KZN maternal mortality rate from all KZN districts. The time of POC test implementation in KZN rural clinics will be obtained from the department of health archives.

Variables: The following is an explanation of the method of Wagner et al (29), applied to our practical analysis. Time series of maternal mortality rate will be assessed using segmented negative binomial regression analysis, which is a method of estimating changes in levels and trends in an outcome associated with an intervention (POC diagnostics). The time series regression equation for this model is as follows:

$$\hat{Y}_t = \beta_0 + \beta_1 \text{ x } time + \beta_2 \text{ x intervention} + \beta_3 \text{ x } time\_after\_intervention + e_t$$

- $\hat{Y}_t$ is the outcome (mean number of deaths per quarter)
- *time* indicates the number of quarters)from the start of the series
- *intervention* is the dummy variable taking the values 0 in the pre-intervention segment and 1 in the post intervention segment
- *time_after_intervention* is 0 in the pre-intervention segment and counts the quarters in the post-intervention segment at time t.
- The coefficient β_0 estimates the base level of the outcome (number of deaths) at the beginning of the series

- β_1 estimates the base trend, i.e. the change in outcome per quarter in the pre intervention segment
- β_2 estimates the change in level of deaths on the post intervention segment
- β_3 estimates the change in trend in deaths in the post-intervention segment
- e_t estimates the error

This model will be used to estimate the impact of HIV and MH related POC diagnostics on maternal mortality in rural KZN.

Objective 5: To evaluate whether introduction POC diagnostics into algorithms for diagnosing maternal patients, improves maternal health for HIV infected women using a systematic review.

The systematic review protocol was developed a priori and was registered in the PROSPERO international prospective register of systematic reviews and in publication (30). PROSPERO record: CRD42014015439, available at: (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015439#.VSfoV-_GPug).

The systematic review will follow recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (31) and the Cochrane Handbook for Intervention Reviews (32). The findings of the systematic review will be disseminated through publication in a peer-reviewed journal and will be formatted according to the specific journal publication guidelines.

Data source: The studies will be selected by evaluation of the inclusion and exclusion criteria. This will be carried out in duplicate and independently by two authors with agreement assessed using kappa statistics.

Objective 6: To develop a model framework and recommendations for improved implementation of POC diagnostics on SA rural PHCs

Guided by the information gathered from the above objectives, we will propose a model framework for improved implementation of POC diagnostics in rural SA PHCs.

Analyses

Qualitative data analysis

Interviews will be conducted with consenting participants in English. Field notes from observations will be written about each observation session. The observations will be used to contextualize the interviews findings and confirm the validity of interpretations.

We will perform a verbatim transcription of all interviews and check transcripts with study participants to seek points of clarification in relation to issues arising from interviews. We will also perform an audit trial for assessing the entire research process. Thematic content analyses will be performed to identify patterns of POC diagnostic key utility areas and deficiencies from respondent's interviews, using NVIVO software. First, participants' responses will be coded into categories which were then grouped into themes. The codes will be grouped into similar concepts that reflect context about local factors that determine healthcare workers and patients' engagement with POC diagnostics. Finally, the identified themes will be validated by the study supervisor. Anticipated themes include: Management; Human resources; Infrastructure; Staff knowledge, Skill; Attitude; Believes; Relevant key stakeholders' perceptions on the quality of POC diagnostics; Relevant key stakeholders' perception on POC diagnostics scale up.

Quantitative analysis

Quantitative data will be entered into a project specific Microsoft Access database and extracted manually onto a categorised table. Data will be grouped in two levels, facility level and individual level. Facility level data will include data from clinic audits and PHC clinic nurses. Inferential statistics will be employed to determine significant differences in the availability of POC diagnostics from the sampled clinics. Standard t-test and ANOVA will be used to compare means across groups while the Pearson chi-.square (χ^2) test will be used for contingency tables. Factors such as distance to the nearest emergency hospital and clinic size in terms of patient volumes and staff numbers, frequency of use for the diagnostics and level of need for the diagnostics (list of POCT requested by clinic staff during survey) will be taken into account. The reliability and accuracy of the POCT test results versus the laboratory gold standard will be estimated along with 95% confidence intervals. Table 1 show variables and analysis for the data obtained from the audit. Systematic review analysis will follow relevant the PRISMA guidelines as stipulated in the published protocol (30).

All quantitative data will be processed and analysed using Stata 13.0 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp L). Descriptive statistics which include frequency distribution, percentages and percentiles, means and standard deviations and cross-tabulations will be used to describe the characteristics of POC diagnostic service in rural KZN. 95% confidence intervals will be constructed around point estimates given the sampling design.

Limitations

We will address any missing data using appropriate statistical methods (33). Data can be missed for many reasons, such as on occasions when a participant did not show up to participate in a study; or one group had more participants than another; or a device did not record the data correctly. The nature of missing data will determine the statistical analysis methods to be employed.

We will undertake a careful and prolonged planning of the study to reduce or eliminate potential sources of bias including sampling bias, recall bias and reporting bias. Recall bias can be introduced in qualitative the data collection stage of investigation, presenting a major threat to the internal validity and credibility of the study. To overcome this limitation in this study, participants will be provided with enough time before answering the question, to reflect and think through a sequence of events in their professional history. The risk of bias for (e.g., internal validity) of systematic review included studies will be evaluated using the Cochrane Risk of Bias tool (32).

ETHICS AND DESSEMINATION

Ethical principles and patient informed consent

The study is being conducted in accordance with the Helsinki Declaration. Permission letters were obtained from all study site managers: KZN health district managers and KZN National Health Laboratory manager. Written consent authorization will be obtained from all study participants prior to any study procedures being done. Participants will be given a copy of the consent form for their record. The consent process will be documented. Participation will be voluntary and each subject will be able to drop out at any time for any reason. All discordant

HIV test results will be reported to the clinic, relevant clinic staff will recall the patients involved for second sample collection and retest by the laboratory.

Legal principles

All personal data will be eliminated. All electronic data of the complete, coded documents will be saved on a protected server which can only be accessed by the members of the internal study team. The paper for of the document will be stored in archives closed for external persons. Data will be kept anonymised kept strictly confidential in storage for two year post completion of the study. No identifying data will be published.

Dissemination of study findings

With this study, our aim is to influence rural PHC policy by translating research evidence to relevant stakeholders. Knowledge translation would be a key aspect of the study, where we intend to disseminate findings to contribute evidence to inform policy makers regarding guidelines for the adoption of new POC diagnostics devices and possible scaling-up the use of POC diagnostic services, for improvement of HIV and maternal health care in rural resource limited settings.

Study timeline

Table 3 depicts the study timeline for each of the study objectives.

Table 3: Study time-line

Objectives	Data collection	Data entry and cleaning	Data analysis	Reporting
Objective 1	April to August 2015	September 2015 to March 2016	March 2016 to April 2016	May 2016
Objective 2	October to December 2015	January 2016 to March 2016	April 2016	July 2016
Objective 3	November to December 2015	December 2015 to January 2016	February to March 2016	May 2016
Objective 4	April 2015 to April 2016	May to June 2016	July 2016	September 2016
Objective 5	October 2015	November 2015	December 2015 to February 2016	March 2016
Objective 6	May 2016	June 2016	July 2016	October 2016

Acknowledgements

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Authors' contributions

TPMT, BS and PKD conceptualised, design the study. TPMT produced the first draft of the manuscript. BS and PKD commented on this draft and contributed to the final version. All authors read and approved the final manuscript.

Competing interests

None declared

Ethical approval

The protocol was approved by the University of KwaZulu Natal, Biomedical Research Ethics Committee (Ref: BE484/14) and the KwaZulu Natal Department of Health Ethics Committee (Ref: HRKM 40/15).

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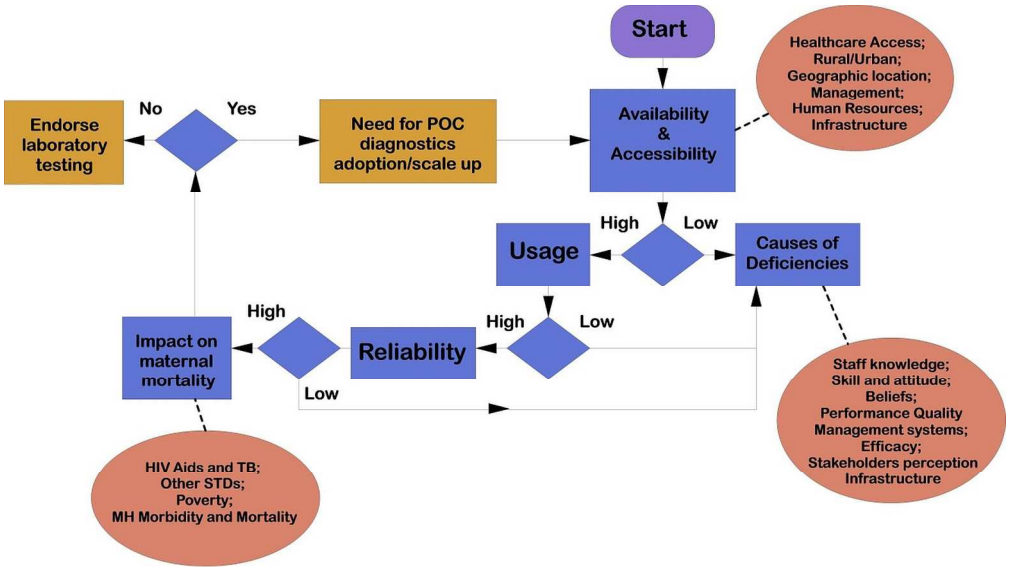

A theoretical framework underpinning this study, program evaluation theory adapted to the local context
160x90mm (300 x 300 DPI)

University of KwaZulu Natal, Durban, School of Nursing and Public Health, Discipline of Public Health Medicine

Title: *Evaluating the accessibility and utility of HIV-related point of care (POC) diagnostics for maternal health in rural South Africa*

PHC POC Diagnostics Services Survey tool

District code:	**Clinic code:**
District name:	**Clinic name:**
Assessors name:	**Date:**

A	**Clinic size and staffing**	
A1	Which of the following healthcare professional are in your clinic?	*(Choose from list below)* ○ Drs: number_____ ○ Staff Nurses: Number_____ ○ PHC Specialist Nurse_____ ○ Sisters (Professional Nurse)_____ ○ Other (Specify)_____
A2	Which of the following describe your role?	*(Choose from list below)* ○ Dr ○ Staff Nurse ○ Specialist Nurse ○ Sister (Professional Nurse) ○ Other (Specify)_____
A3	What is an average number of MH patients admitted in the clinic per week?	*(Write number)*

A4	How many hours per week do you work (on average)?	*(Write number)*
B	**POC diagnostics service linkage to healthcare**	
B1	How many kilometers to your nearest emergency department that admits patients to hospital?	*(Write number)*
B2	How many kilometers to your nearest town/city?	*(Write number)*
C	**Length of time for blood test**	
C1	How long does it typically take to get results from a routine blood test, such as full blood count?	*(Choose from the following)* ○ One day or more: _____days ○ Less than 1 day: _____ hours ○ Already use a POC diagnostics for this test, so it is immediately done
D	**Staff POC diagnostics competency**	
D1	What year did you qualify as a Healthcare professional?	*(Write full year)*
D2	Please name up to five conditions which a POC test could help you make a **diagnosis**. Please list the conditions irrespective of whether or not POC test currently exist	○ _____ ○ _____ ○ _____ ○ _____ ○ _____ **I do not think POC tests would help me make a diagnosis (please tick box)** ☐
D3	Please name up to five conditions which a POC test could help you make a **monitor**. Please list the conditions irrespective of whether or not POC test currently exist	○ _____ ○ _____ ○ _____ ○ _____ ○ _____ **I do not think POC tests would help me** ☐

		monitor a disease (please tick box)
D4	Please name up to five conditions which a POC test could help you make a **reducing referrals for specialty care or hospital admission**. Please list the conditions irrespective of whether or not POC test currently exist	○ _____ ○ _____ ○ _____ ○ _____ ○ _____ **I do not think POC tests would help me reduce referrals for specialty care or hospital admission (please box)** ☐

E. POCTs used *Please select the answer that best matches your views about current or potential use of point of care tests (POCTs)*				
	This test **is** currently available as a point of care test (POCT) in my clinic		This test **is not** currently available as a point of care test (POCT) in my clinic	
	(1) I **do** use this test	*(2)* I **do not** use this test	*(3)* I **would** use this test	*(4)* I **would not** use this test
TESTS ON BLOOD				
Cardiovascular				
Creatinine				
Potassium				
Sodium				
Total cholesterol				
HDL/LDL cholesterols				
Triglycerides				
Calcium				
Uric Acid				
BNP (B-natriuretic peptide)				
D-dimer				
Troponin				
Endocrine				
Blood glucose				
HbA1c				
TSH (thyroid stimulating hormone)				

Free T4 or T3				
Haematology				
INR				
Haemoglobin				
White cell count				
Platelet count				
Prothrombin time				
Infection related				
CRP (C-reactive protein)				
Procalcitonin				
HIV blood test				
Syphilis				
Hepatitis B				
Liver				
AST/ALT				
Alkaline phosphatase				
Bilirubin				
Gamma GT (ɣ-glutamyltransferase)				
Albumin				
Other (blood)				
ESR (*Erythrocyte sedimentation rate)*				
CA125				
PSA (Prostate Specific Antigen)				
Vitamin D				
Vitamin B12				
Folate				
Quantitative Beta HCG (Human chorionic gonadotropin)				
Rheumatoid factor				
ANA (anti-nuclear antibodies)				

	This test **is** currently available as a point of care test (POCT) in my clinic		This test **is not** currently available as a point of care test (POCT) in my clinic	
	(1) I **do** use this test	*(2)* I **do not** use this test	*(3)* I **would** use this test	*(4)* I **would not** use this test
RESPIRATORY SAMPLES				
Throat swab for				

Group A Streptococci				
Nasal swab for MRSA				
Nose/throat swab for influenza				
TESTS ON URINE OR GENITAL FLUIDS				
Urine pregnancy test				
Urine leukocytes or nitrite				
Chlamydia				
Gonorrhoea				
Urine albumin:creatinine ratio				
Urine total protein				
Urine protein:creatinine ratio				
TESTS ON FAECES				
Faecal occult blood				
Faecal calprotectin				
OTHER TESTS WE HAVE NOT LISTED HERE				

F. Frequency of POCT usage

Below is a list of point of care tests (POCTS) you indicated that you would use or currently use in your practice. Please tell us how often you would use or do use these

	More than once per day	Daily	Weekly	Monthly	Once per year or less
TESTS ON BLOOD					
Cardiovascular					
Creatinine					
Potassium					
Sodium					
Total cholesterol					
HDL/LDL cholesterols					
Triglycerides					
Calcium					

Uric Acid					
BNP (B-natriuretic peptide)					
D-dimer					
Troponin					
Endocrine					
Blood glucose					
HbA1c					
TSH (thyroid stimulating hormone)					
Free T4 or T3					
Haematology					
INR					
Haemoglobin					
White cell count					
Platelet count					
Prothrombin time					
Infection related					
CRP (C-reactive protein)					
Procalcitonin					
HIV blood test					
Syphilis					
Hepatitis B					
Liver					
AST/ALT					
Alkaline phosphatase					
Bilirubin					
Gamma GT (ɣ-glutamyltransferase)					
Albumin					
Other (blood)					
ESR (*Erythrocyte sedimentation rate)*					
CA125					
PSA (Prostate Specific Antigen)					
Vitamin D					

Vitamin B12					
Folate					
Quantitative Beta HCG (Human chorionic gonadotropin)					
Rheumatoid factor					
ANA (anti-nuclear antibodies)					

	More than once per day	Daily	Weekly	Monthly	Once per year or less
RESPIRATORY SAMPLES					
Throat swab for Group A Streptococci					
Nasal swab for MRSA					
Nose/throat swab for influenza					
TESTS ON URINE OR GENITAL FLUIDS					
Urine pregnancy test					
Urine leukocytes or nitrite					
Chlamydia					
Gonorrhoea					
Urine albumin:creatinine ratio					
Urine total protein					
Urine protein:creatinine ratio					
TESTS ON FAECES					
Faecal occult blood					
Faecal calprotectin					
OTHER TESTS WE HAVE NOT LISTED HERE					

Do you have suggestions for new POC Tests?

What POC tests might make your job easier?